BENZOYL PEROXIDE

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SUMMARY

The mode of action of benzoyl peroxide in acne is threefold, i.e. sebostatic, comedolytic and inhibitory to *P. acnes* in-vivo.

Benzoyl peroxide is the topical treatment of choice in acne vulgaris. This agent is well tolerated by most patients. Primary irritant dermatitis can be avoided by less frequent application and the true incidence of contact sensitivity is low. The gel preparation has achieved a high degree of cosmetic acceptability. A synergistic effect with retinoic acid can be demonstrated.

Tolerance to benzoyl peroxide develops in most subjects necessitating more vigorous therapy, usually after two or three weeks of treatment. Many acne sufferers with mild or moderate disease can avoid long-term oral antibiotic treatment by the judicious use of benzoyl peroxide topically.

HISTORY

Benzoyl peroxide, which is derived from a by-product of coal tar, was first used as a non-irritating oxidizing antiseptic by Loevenhart in 1905 (1). Subsequently, there was little dermatological interest in this compound and its main use was a bleaching agent for flour. Lyon & Reynolds, in 1929, claimed that benzoyl peroxide promoted wound healing (2). In 1934 Peck and Chargin (3) described the use of topical benzoyl peroxide in sycosis vulgaris and Leake, in 1942, claimed that benzoyl peroxide, when applied locally to wounds acted as a long-lasting oxidizing antiseptic with lack of local irritant effects (4). In addition, healing was promoted and there was also a local anaesthetic action to relieve pain and local irritation.

Modern interest in benzoyl peroxide was stimulated by Pace in 1965 and the use of benzoyl peroxide, combined with sulphur in a cream formulation, was used in the treatment of acne vulgaris (5). Following this development, the pharmaceutical industry found a way of preparing stable lotions of benzoyl peroxide. Combination therapy was also developed with sulphur and chlorhydroxyquinoline. More recent developments include the incorporation of benzoyl peroxide into a gel base to facilitate bioavailability.

PHYSICAL PROPERTIES OF BENZOYL PEROXIDE

Chemically, benzoyl peroxide is $C_{14}H_{10}O_4$ and the structural formula is shown in Fig. 1. Benzoyl peroxide is a crystalline solid of poor solubility in water and mineral oil. It is said to be stable at room temperature, but becomes inflammable and explosive if confined or subjected to heat or friction. It is a powerful oxidizing agent and is now used widely in industry as a catalyst for polyester and acrylic resins and as a bleaching agent for edible oils and flour (6).

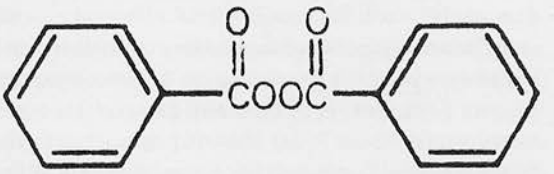

Fig. 1. Benzoyl peroxide — structural formula.

MODE OF ACTION

There are three factors thought to be important in the pathogenesis of acne, namely, sebaceous gland hyperactivity rate, obstruction to the pilo-sebaceous apparatus by excessive keratinization in the infrainfundibulum and, generation of inflammatory agents by *Propionibacterium acnes*. The role of free fatty acids in the pathogenesis of acne vulgaris is now disputed, but a reduction in skin surface free fatty acid levels accompanies effective oral antibiotic treatment and is also seen following the use of topical antibiotics and antibacterial substances applied to the skin in acne.

There is little data on the effect of benzoyl peroxide on sebum excretion rate. However, van Doris Fanta and co-workers showed that benzoyl peroxide was "sebostatic" by the use of autoradiography (7).

It has been shown that benzoyl peroxide will produce scaling after 10—14 days of regular application to the skin (8), and the degree of peeling is dose-dependent in that a 10% concentration produces

more peeling than a 5% concentration (9). Plewig & Kligman have also shown that benzoyl peroxide has about 50% of the comedolytic activity of retinoic acid in a rabbit ear assay.

Fulton and co-workers reported bacteriological and skin surface lipid biochemical changes following topical application of benzoyl peroxide in an alcoholic gel formulation (10, 11). These workers showed that bacterial cultures of *P. acnes* were inhibited by benzoyl peroxide and after two weeks of daily exposure to this oxidizing agent freshly-excreted sebum became essentially sterile. At the same time, benzoyl peroxide produced a more rapid and more dramatic reduction in the free fatty acid — fatty ester ratio measured by infrared spectroscopy — than systemic tetracycline. Furthermore, Plewig and Kligman have claimed that it requires about six weeks of treatment with oral tetracycline to effect *P. acnes* and free fatty acids to the degree seen after two weeks treatment with topical benzoyl peroxide gel (9).

Kligman and co-workers have also demonstrated that benzoyl peroxide is a potent antimicrobial agent exerting an immediate antibacterial effect on normal skin flora and capable of suppressing strongly a dense population of skin microorganisms at concentrations of both 2.5% and 5%. This antibacterial effect could be shown to persist for at least 48 hours, even in the face of optimal conditions for bacterial growth. Kligman and his colleagues concluded that benzoyl peroxide was unusual in that it combined potent bactericidal effects with prolonged activity. Comparable compounds with an instant bactericidal activity, such as Povidone iodine and alcohol, had rather short-lived activities on human skin of the order of six hours. Benzoyl peroxide thus offers broad spectrum prolonged bactericidal activity (12). This work by Kligman et al. was performed with an alcoholic gel base which in itself exerts a drying and astringent effect to enhance the clinical benefit of benzoyl peroxide. The topical drying effect of benzoyl peroxide itself may also be important bacteriologically.

In summary, benzoyl peroxide has three principal actions in acne. It may act as a depressant of sebum production; it can be shown to be comedolytic and has powerful antibacterial activities suppressing *P. acnes* in-vivo.

Benzoyl peroxide has other pharmacological properties which may be important to a lesser degree in facilitating its beneficial action in acne. Mild erythema, due to a local increase in blood flow, is a feature of its topical use, especially in the initial stages of treatment and Vasarinsh regards benzoyl peroxide as a dermal irritant (8). It is interesting that the high vascularity of the face may protect against contact sensitization, and benzoyl peroxide can be shown to have strong sensitizing potential. However, in practice, there have not been widespread sensitivity problems attending its use (12).

Leake has claimed that benzoyl peroxide has local anaesthetic properties (4). The same author has also claimed that this compound is able to promote healing.

Benzoyl peroxide is known to be capable of bleaching hair and this effect can be utilized clinically in hirsute women with acne.

ADVERSE EFFECTS OF BENZOYL PEROXIDE

Benzoyl peroxide, when used as a bleaching agent, is converted into benzoic acid. Benzoyl peroxide has found general acceptance as a food additive and appears to be nontoxic in experimental animals (6). Contact dermatitis occurs with an incidence usually varying between 1% and 2.5% and the incidence depends to some extent on the base (6). The highest recorded incidence of sensitivity was 3.2% (7). Patch test reactions may be urticarial and cross reactions with cinnamon and benzoic acid have been noted (13). Some patients experience a transient burning when using this preparation, whilst others develop an erythema, especially in the early stages of treatment. This may be marked enough to cause cessation of treatment, although no evidence of true contact sensitivity can be found in these subjects.

After an initial phase of redness and scaling, the skin rapidly accommodates and this phenomenon of tolerance has been commented on by Vasarinsh and Plewig & Kligman (8, 9). A primary irritant dermatitis due to benzoyl peroxide usually responds to either withdrawal of the irritating agent, or, more commonly, to the less frequent application of the medicament. It is interesting that most cases of contact dermatitis to benzoyl peroxide have occurred in female patients (11).

COMBINATION THERAPY

Ointments containing benzoyl peroxide and chlorhydroxyquinoline have been available since 1930 (9). Plewig and Kligman regard these ointments as messy and of questionable stability and claimed that chlorhydroxyquinoline does not add to the effectiveness of

benzoyl peroxide in acne (9). On the other hand, Ede showed that a combination of benzoyl peroxide and chlorhydroxyquinoline was marginally superior clinically to benzoyl peroxide alone (14). There is also a divergence of view on whether sulphur should be combined with benzoyl peroxide. Whilst Plewig and Kligman (9) claimed that elemental sulphur antagonizes the comedolytic activity of benzoyl peroxide, Fulton and Bradley (11) stated that sulphur is not necessary for the beneficial response from benzoyl peroxide, but does augment the latter's effect.

RETINOIC ACID AND BENZOYL PEROXIDE

Retinoic acid and benzoyl peroxide are chemically incompatible, as the latter will oxidize the former. However, there has been some work recently on the use of retinoic acid applied, for instance, on the skin in the morning, followed by benzoyl peroxide applied subsequently on the skin in the evening in acne subjects. The rationale for this therapy is that retinoic acid may make the skin more permeable and also have a greater comedolytic effect than benzoyl peroxide. It has been claimed that after three months of such treatment the proportion of patients achieving excellent improvement is about twice that with combined therapy than with benzoyl peroxide alone (9). Fulton and co-workers (11) further stated that this combination treatment is the treatment of choice for mild and moderate degrees of acne and obviates the need for systemic antibiotics in most patients.

CORTICOSTEROID BENZOYL PEROXIDE COMBINATIONS

The author has no experience with hydrocortisone-benzoyl peroxide formulations, but this may be an interesting pharmacological development if stable preparations can be produced.

CLINICAL STUDIES

There is now an abundance of clinical data on the topical use of benzoyl peroxide in acne, and the results of some of these studies are summarized in the Table. Vasarinsh showed clearly in a double-blind study that a 5% benzoyl peroxide lotion containing 2% sulphur was more effective than 5% benzoyl peroxide lotion alone (8). It has recently been shown by Cotterill that a 5% benzoyl peroxide gel (Panoxyl-5 gel, Stiefel Laboratories) is clinically superior in papular-pustular acne to a 5% benzoyl peroxide lotion (15). Many clinical studies have been uncontrolled, but Liddell in 1974, who stressed the cosmetic acceptability of Panoxyl gel, presented data on a total of 133 patients who had been treated topically for a month with either Panoxyl-5 or -10 gel and about 80% improved (16). Hare also stressed the cosmetic preference by his patients for benzoyl peroxide gel. Thus 35% of patients using a retinoic acid solution were pleased with their results compared with 75% of those using benzoyl peroxide, gel. Moreover, the retinoic acid seemed more difficult to use (17). Van Doris Fanta and colleagues treated 63 patients with 5—10% Panoxyl gel for a period of 2—4 months and 80% of patients with papular-pustular acne improved (7).

Table. *Benzoyl peroxide gel data.*

Author	No. of patients	Preparation used	Duration of treatment	% improved
Liddell, 1974	133	Panoxyl '5' and '10' gel	1 month	≅ 80%
van Doris Fanta et al, 1976	63	5—10% Panoxyl gel	2—4 months	≅ 80%
Kuflik, 1976	53	5 and 10 Benzagel	11 months	≅ 92%
Meigel & Pruckner, 1977	31	Panoxyl '5' and '10' gel	2 months	≅ 75%
Constantino et al, 1977	72	Panoxyl '5' and '10' gel	3 months	≅ 80%

Kuflik treated 53 patients with a 5—10% benzoyl peroxide gel preparation for up to 11 months and about 92% of his subjects improved (18). Meigel and Pruckner treated 31 patients with Panoxyl-5 and -10 gel for two months and 75% of their patients with papular-pustular acne improved (19).

Fulton and his co-workers have stressed that the mechanism of action of benzoyl peroxide is different to that of topical Vitamin-A-acid and combination therapy was evaluated by his group in over 1.000 patients. These workers claimed that combination treatment was more effective than either treatment alone and resulted in resolution of the acne usually within three months.

Finally, I should like to present some data on benzoyl peroxide from Dr. Cunliffe's laboratory in Leeds (20). Dr. Cunliffe and his colleagues studied 72 pati-

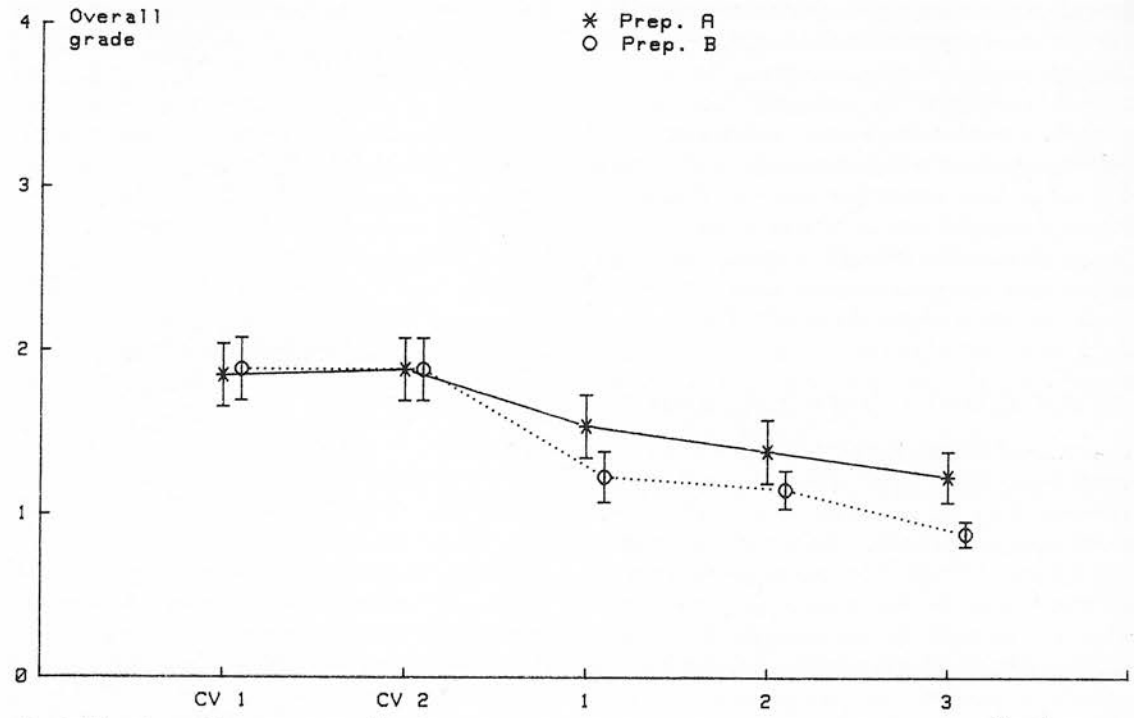

Fig. 2. The effect of therapy on overall grade.

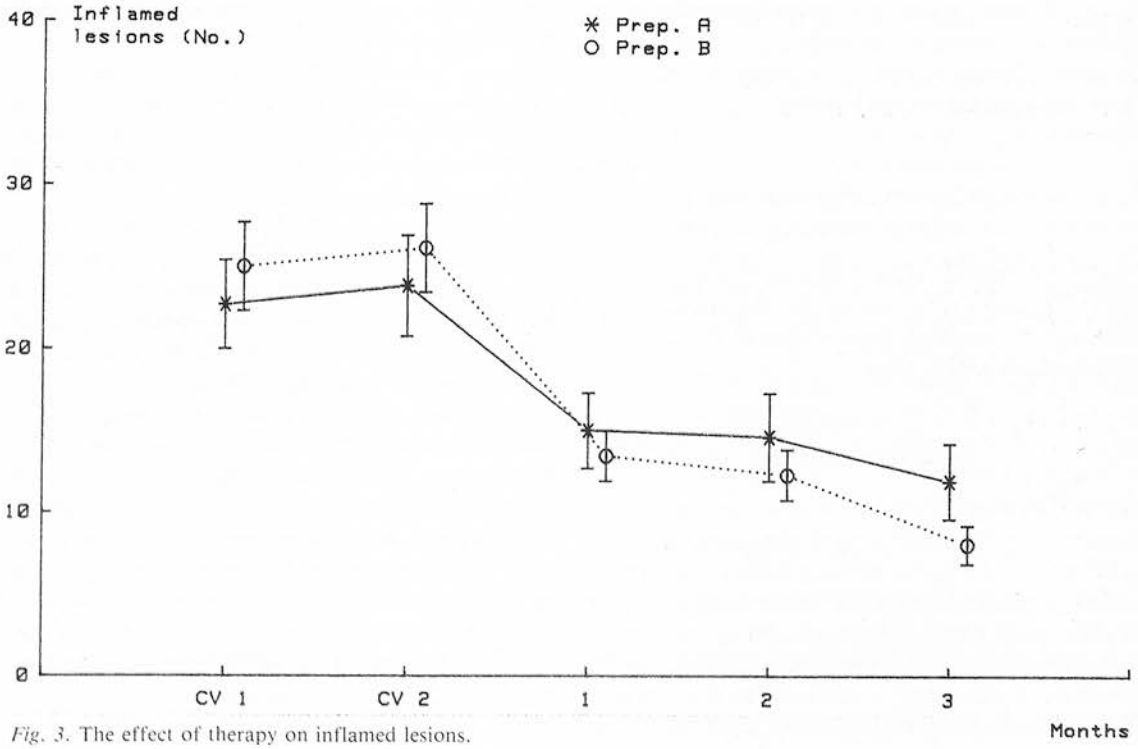

Fig. 3. The effect of therapy on inflamed lesions.

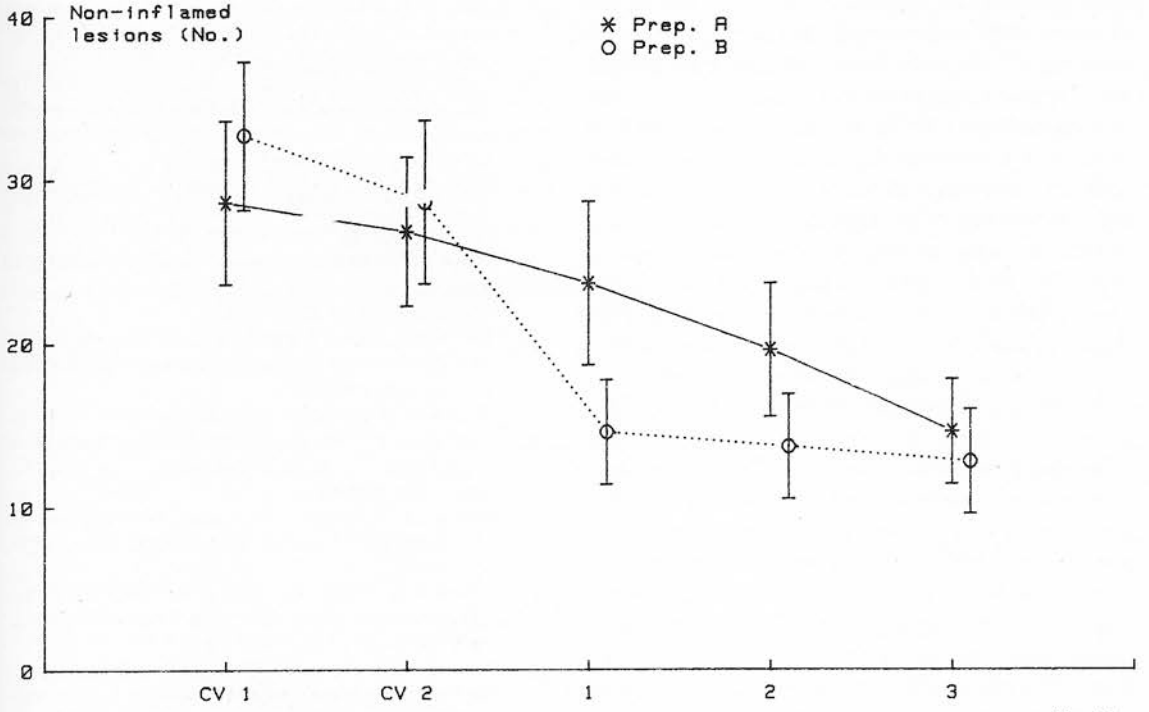

Fig. 4. The effect of therapy on non-inflamed lesions.

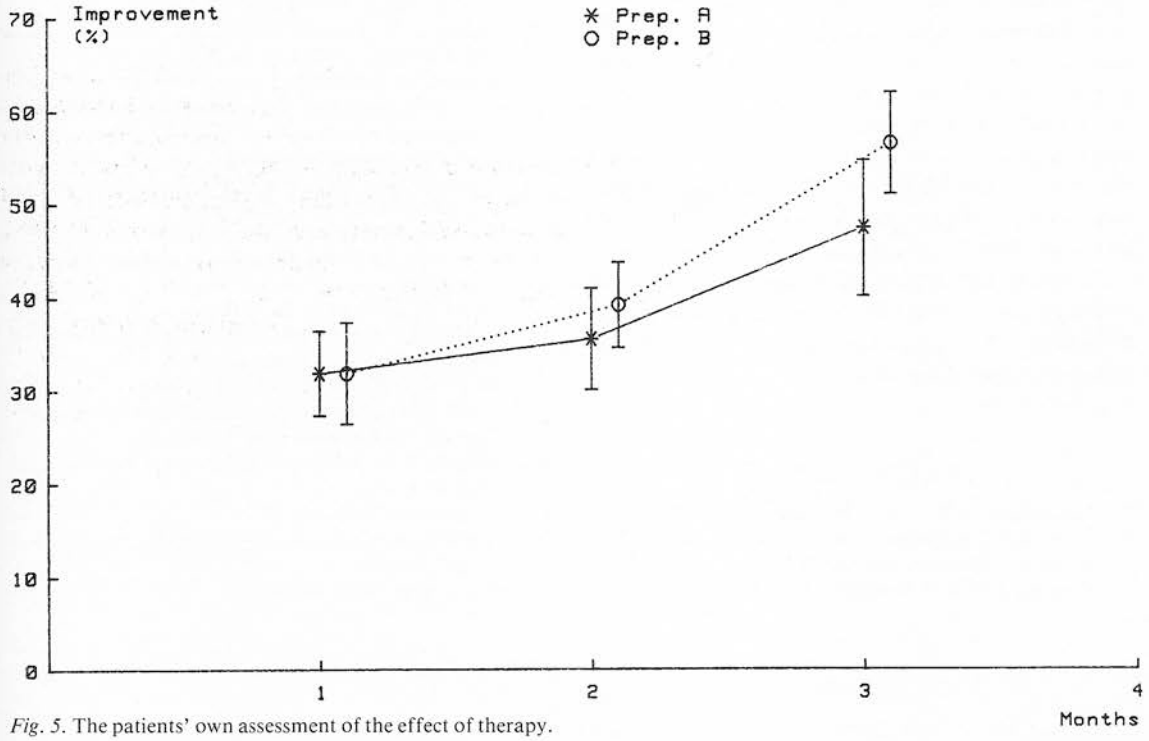

Fig. 5. The patients' own assessment of the effect of therapy.

ents, 30 males and 42 females, aged between 14 and 18 years. None of the patients had received any treatment for one month before the investigation. The patients were seen on five occasions in all. There were two control visits within two or three days of each other and three visits at monthly invervals during treatment thereafter. At each visit an overall assessment was made of the grade of acne on an arbitrary zero to five scale, a count of five representing severe acne. The total number of blackheads, whiteheads (non-inflamed lesions) and pustules, papules and nodules (inflamed lesions) were counted. The patients were also asked to assess the severity of their acne. After the control visits the patients were matched into pairs with respect to overall grading. One subject from each pair received preparation A and the other preparation B, which looked the same and were dispensed in identical bottles. The subjects were asked to use the medicament on the acne lesions twice a day. Preparation A was benzoyl peroxide 10% in a cream base, with hydroxyquinoline sulphate (Quinoderm); preparation B was benzoyl peroxide gel 5% (Panoxyl-5 gel). The results are shown in Figs. 2—5. It can be seen that there were no significant differences between the two groups at the control visits as far as overall grade and numbers of inflamed and non-inflamed lesions were concerned, but by the first, second and third months of treatment, several statistically significant changes had appeared. Preparation B showed a consistent improvement in all variables compared to preparation A. It should be noted that at the end of one month, group B patients showed a greater improvement in the overall grade of acne and a greater reduction in the number of blackheads and whiteheads compared to group A patients. The patients' own assessments favoured preparation B.

As far as side effects were concerned, both the erythema and scaling that occurred in both groups decreased with continued application. This was confirmed by direct measurement.

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DISCUSSION

Donsky, Toronto: I would like to make a little plug for Dr. William Pace in London, Ontario. This man worked with benzoyl peroxide for years and years and nobody would listen to him when he was claiming such excellent results. Our results with this preparation have just been fantastic as well. The way we avoid the problem with irritation is to start with a very low dosage, such as 2.5%. Our patients are instructed to apply it for 15 minutes on the first evening and then just double the time each subsequent evening until they leave it on for four hours. Then they can leave it on all night. Then, they can begin using first the 3%, then the 10% and finally the 20% preparations. This has worked out very very well for us and that benzoyl peroxide remains a very potent therapeutic agent for us.